REMARKS

This is in response to the Official Action dated January 25, 2007. Claims 1-32; 60 and 88-100 are currently pending. All references, which are discussed in this response and were not previously considered by the Examiner, are submitted in a supplemental Information Disclosure Statement concurrently filed with this response.

I. New Claims 101-107

Applicants have added new Claims 101-107, which are directed to specific compounds disclosed in the originally filed application. Claims 101 and 105 are supported by compound 112 on page 52. Claim 102 is supported by the table of exemplary compounds found on pages 39-81. Claim 103 is supported by compound 372 on page 80. Claim 104 is supported by compounds 24 and 25 on page 42. Claim 106 is supported by synthetic intermediate 18 on page 94 and compound 20 on page 95. Claim 107 is supported by synthetic intermediate 10 on page 86.

The new claims present no new matter and are supported by the specification as originally filed. Applicants respectfully request entry thereof.

II. Amendments to the specification

The specification is amended herein to correct an error in the structure of compound 20 on page 95. The corrected structure is supported by the name of compound 20 and the synthetic method such as the starting material and the yield. The Applicants respectfully requested the entry of the amendment.

III. Claims rejections—35 USC §112

A. Indefiniteness.

Claim 1 stands rejected under 35 U.S.C. § 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. In particular, the Examiner rejected the recitation "derivative" in Claim 1.

To simplify the issues, the phrase "derivative" has been modified to read "salt, ester, or salt of such ester thereof." Support is found in the specification where the term

"pharmaceutically acceptable derivative" is defined as: "any **salt, ester, or salt of such ester, of such compound**, or any other adduct or derivative which, upon administration to a patient, is capable of providing (directly or indirectly) a compound as otherwise described herein, or a metabolite or residue thereof. Pharmaceutically acceptable derivatives thus include pro-drugs. A pro-drug is a derivative of a compound, usually with significantly reduced pharmacological activity, which contains an additional moiety which is susceptible to removal *in vivo* yielding the parent molecule as the pharmacologically active species." *See* the present application, page 18, paragraph [0063] (emphasis added). Accordingly, it is respectfully submitted that claim 1 is now clearly defined as required by the 35 USC § 112, second paragraph, and it is respectfully requested that this rejection be withdrawn.

B. Enablement

Claims 29-32 (directed to compositions), 60 and 88-100 (directed to methods of treatment) stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. This rejection is respectfully traversed.

The test of enablement under 35 USC §112, first paragraph, is whether one skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation. *See, e.g.,* MPEP 2164.01. Further, it is well settled that "a patent need not teach, and preferably omits, what is well known in the art". *Id.* In addition, in order to make a rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *See* MPEP 2164.04. It is also specifically noted that a specification which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the claimed subject matter must be taken as in compliance with the enablement requirement **unless there is a reason to doubt the objective truth of the statements** contained therein.

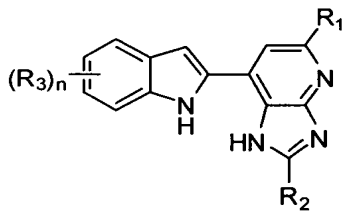
The *Wands* factors are usually considered in determining whether undue experimentation would be required to make or use the claimed invention. Hence, these factors are discussed in further detail below.

A. The breadth of the claims. It is alleged in the Official Action that the scope of the

claims is broad because the claims involve both numerous compounds and numerous diseases. *See* Official Action, page 4. Applicants respectfully disagree. The claims in the present application are well focused by a clearly defined core structure. Hence, this factor weighs in favor of the applicants.

Claims 60 and 88-100 are directed to the treatment of three types of diseases: (1) inflammatory disorders, (2) autoimmune disorders and (3) proliferative disorders. These three diseases are well supported by the disclosure of the present application. *See* the present application, pages 30-36, paragraphs [0090] to [0108].

In addition, claim 1 specifies a well-defined core structure in formula (I):



This core structure has an indole ring linked to the imidazopyridine ring through a single bond. The core structure includes only three groups of substituents. Still further, the location of substituents R_1 and R_2 are specified on the imidazopyridine ring. Numerous examples (*e.g.*, 300 to 400) of the genus are given. In view of all of these features, it is respectfully submitted that the claims are not extremely broad as characterized in the Official Action, and respectfully submitted that this factor weighs in favor of the applicants.

B. The nature of the invention and the state of the prior art. Applicants respectfully submit that these two factors weigh in favor of the applicant.

The references cited by the Examiner to establish the state of prior art were published in 1975 and 1986, and therefore they do not represent the state of prior art at the time of filing the instant application in 2002. Between 1986 and 2002, there were significant developments in the use of small organic compounds to treat the three types of disorders claimed in the present application. A few examples of issued patents in this area are:

(1) Examples of treating inflammatory disorders:

US Patent No. 4,891,374, Imidazo- and triazolothiadiazines;
US Patent No. 5,342,832, Use of mono and di-inositolphosphates

for treating inflammation;

US Patent No. 5,492,915, Substituted quinolyl compounds exhibiting selective leukotriene B_4 antagonist activity.

(2) Examples of treating autoimmue disorders:

US Patent No. 5,360,794, Disubstituted and deoxy disubstituted derivatives of α-D-mannofuranosides and β-L-gulofuranosides having anti-inflammatory and anti-proliferative activity;

US Patent No. 5,981,536, Use of xanthine derivatives for the modulation of apoptosis;

(3) Examples of treating proliferative disorders:

US Patent No. 5,656,654, Arylidene and heteroarylidene oxindole derivatives and process for their preparation;

US Patent No. 5,565,452, 9-amino-pyridazino[4',5':3,4]pyrrolo-[2,1-A]isoquinolines and the use thereof for the production of pharmaceutical preparations;

US Patent No. 5,880,141, Benzylidene-Z-indoline compounds for the treatment of disease.

Therefore, at the time of the filing the instant application, a large number of small organic compounds other than deazapurine had been established for the treatment of the disorders claimed in the present invention. In view of this additional evidence, it is submitted that these two factors, the nature of the invention and the state of the art, weigh in favor of applicants.

C. The level of skill. The action suggests that one of ordinary skill in the art with which the present invention is concerned is a physician with a MD degree and several years of experience. *See* Official Action, page, page 4. Applicants strongly disagree.

The present invention involves multiple art areas, including organic synthesis, compound screening, compound formulation, and administration. The Federal Circuit's predecessor long ago explained that, to the extent an invention involves multiple fields, ***the applicants need only enable the specialist in each art*** to carry out that aspect of the invention on which he or she is most qualified to work. *See, e.g., In re Naquin,* 398 F.2d 863, 866, 158 USPQ 317, 319 (CCPA 1968). Synthesis of compounds, screening compounds to determine the biological activity, and formulation into suitable dosage are all areas of separate expertise, in which each specialist would have an advanced degree and several years of work experience. A physician with a MD

degree and several years of clinical experience may indeed be involved in the treatment of patients, including the selection, monitoring, and adjustment of particular dosages, but need not be involved in the synthesis, selection, and formulation of the active agent (all of which would be carried out in separate departments, by individual specialists, in a pharmaceutical company supplying a product to that physician). Therefore, it is respectfully submitted that the Examiner's definition of the level of ordinary skill is erroneous and should be modified to include these multiple areas of expertise. When so modified, it is respectfully submitted that this factor weighs in favor of the applicants.

D. The level of predictability in the art. The action alleges that the present invention is concerned with an unpredictable art, since physiological activity is generally considered to be an unpredictable factor. *See* Official Action, page 4.

Applicants respectfully disagree. Although the biological sciences are generally categorized as "unpredictable", the courts have long emphasized that the issue is not predictability *per se*, but rather the type of work and experimentation acceptable in the particular field, or fields, with which the invention is concerned. For example, in *In re Angstadt,* the Court of Customs and Patent Appeals cautioned that:

> If [our prior decision stands] for the proposition that the disclosure must provide "guidance which will enable one skilled in the art to determine, *with reasonable certainty before performing the reaction,* whether the claimed product will be obtained,... then *all* "experimentation" is "undue," since the term "experimentation" implies that the success of the particular activity is *uncertain.* Such a proposition is contrary to the basic policy of the patent act...."

In re Angstadt, 537 F. 2d 498, 503, 190 USPQ 214, 219 (CCPA 1976). The court went on to emphasize that "the key word is "undue," not "experimentation." *Id* at 504, 190 USPQ at 219.

In particular, the courts have recognized that the pharmaceutical field is one in which quite substantial amounts of experimentation and research are considered "routine" rather than "undue. " For example, the Court of Appeals for the Federal Circuit has specifically noted that:

> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, ***necessarily includes the expectation of further research and development.*** The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans.

In re Brana, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995) (emphasis added). Hence, it is

submitted that the level of predictability of the present invention is not undue, and that this factor weighs in favor of the applicants.

E. The amount of direction or guidance presented. The Examiner alleges that there is no guideline for determining different doses needed to treat the three types of disorders claimed. *See* Official Action, page 3. In addition, the Examiner also states that it is unclear if the biological assay described on pages 177 and 178 is correlated to the treatment of the claimed diseases. *Id.*

Applicants respectfully disagree and submit that the specification provides *ample* guidance for practicing the claimed invention. It is well established that it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. MEPP 2164.01 (c). Furthermore, if one skilled in the art, based on the knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or methods of use without undue experimentation, this would be sufficient to satisfy the enablement requirement. *Id.*

As the Examiner conceded, the present invention provides a detailed description of the pharmaceutical formulation in paragraphs [0078] to [0089] and dosages in paragraph [0096]. Furthermore, as discussed above regarding the state of prior art, the treatment of the disorders with which the invention is concerned are in generally well-established areas, as evidenced by the numerous patents that were already issued at the time the instant application was filed. Moreover, the dosage for the treatment of disorders can always be adjusted by an experienced physician on the basis of the therapeutic effects on individual patients. Therefore, the present invention provides ample guidance and direction regarding the dosage for the three types of disorders of the present invention.

Applicants also disagree with the Examiner's assertion regarding the correlation of the HUVEC assay described on pages 177 and 178 of the specification and the treatment of claimed diseases. It is noted that the issue of "correlation" is dependent on the state of the prior art. MPEP 2164.02. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then the model should be accepted unless the examiner has evidence to the contrary. *Id.* The Federal Circuit has noted that even with evidence that a model does not correlate, the examiner must weigh the evidence for and against correlation and decide

whether one skilled in the art would accept the models as reasonably correlated to the claimed condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ 2d 1436, 1441 (Fed. Cir. 1995).

The present application is concerned with the development of novel therapeutic agents useful for treating three types of disorders. The present application explains that cell adhesion molecules are required for many of the cell-to-cell interactions involved in inflammatory and immune responses. *See, e.g.,* the present application, page 1, paragraph 2. Several adhesion molecules, including E-selectin and ICAM, are induced by cytokines such as IL-1 and TNF, and their expression is mediated by the transcriptional factor, NF-κB. (*See* the present application, page 1, paragraphs 2 and 136 (*See*: NF-κB: a key role in inflammatory diseases, *J. Clin. Investig.* 2001, **107**, 7-11. (Copy submitted concurrently herewith)). The identification of NF-κB as a key factor suggests that NF-κB targeted therapeutics would be beneficial for the treatment of inflammatory and immune disorders. *Id.* In particular, the present application explains that the exaggerated expression of E-selectin and/or ICAM can result in inflammation and has been associated with several inflammatory or autoimmune disorders, and therefore indicating that inhibitors of cell adhesion molecules for the treatment of these diseases. *See Id.* paragraph 3. The HUVEC Assay Protocol of the present invention is used to screen the compounds for cell adhesion of E-selection and ICAM expression, which is clearly demonstrated by the procedures of the assay described on pages 177 and 178 of the specification.

Furthermore, it was well established before the filing date of the present application that ELAM-1 (endothelial cell adhesion molecule-1; also designated as E-selectin) and ICAM are actively involved in the development of inflammatory, autoimmune or proliferative disorders before the filing date of the present application. *See* Yusuf-Makagiansar et al., Inhibition of LFA-1/ICAM-1 and VLA-4/VCAM-1 as a therapeutic approach to inflammation and autoimmune diseases. *Med. Res. Rev.*, 2002, 22, 146-167 (Copy submitted concurrently herewith), and Norton et al., Expression of adhesion molecules in human intestinal graft-*versus*-host disease, *Clin Exp. Immunol.*, 1992, 87, 231-236. (Copy submitted concurrently herewith). Therefore, the ICAM and E-selectin model can be used to support the *in vivo* use of the claimed compounds in the prevention and/or treatment of inflammatory autoimmune and/or proliferative disorders.

In addition, the ICAM and E-selectin assay can also indicate the effect of the compounds of the present invention against cell adhesion molecules involved in proliferative disorders. As

discussed by P. Brodt in *Int. J. Cancer* in 1997, endothelial cell adhesion receptors have been shown to be involved in carcinoma cell adhesion and ultimately in metastasis. *See* P. Brodt et al., Liver Endothelial E-selectin Mediates Carcinoma Cell Adhesion and Promotes Liver Metastasis, *Int. J. Cancer*, 1997, **71**, 612-619 (Copy submitted concurrently herewith). In particular, inhibition of the endothelial cell adhesion receptor E-selectin significantly decreased the degree of metastasis with two highly metastatic human colorectal carcinoma lines HM7 and CX-1. *Id.* Finzel in *Clinical & Experimental Metastasis* in 2004 demonstrates that metastasis in small cell lung carcinoma requires adhesion of tumor cells to the endothelium via ICAM-1. *See* Finzel et al., ICAM-1 supports adhesion of human small-cell lung carcinoma to endothelial cells, *Clinical & Experimental Metastasis,* 2004, **21**, 185-189 (Copy submitted concurrently herewith) Furthermore, Rosette in *Carcinogenesis* in 2005 further confirmed that ICAM-1 is associated with the occurrence of metastases in breast cancer. *See* Rosette et al., Role of ICAM-1 in Invasion of Human Breast Cancer Cells, *Carcinogenesis*, 2005, **26**, 943-950 (Copy submitted concurrently herewith)

In addition, the correlation of activity between E-selectin and ICAM and the therapeutic treatment of inflammatory, autoimmune, and/or proliferative disorders is well established in the issued patent literature. Examples of patents demonstrating this correlation include but are not limited to:

US Patent No. 6,831,065 Anti-inflammatory compounds and uses thereof; (*See e.g.* Claim 8: using E-selectin for treatment of inflammatory disorder)

US Patent No. 6,521,654, Wehner, Substituted imidazolidine derivatives, their preparation, their use and pharmaceutical preparations including them (*See e.g.* Claim 18: using E-Selectin and ICAM model for treatment of autoimmune disorder)

US Patent No. 5,632,991, Antibodies specific for E-selectin and the uses thereof (*See e.g.* Claim 12: using E-selectin for treatment of proliferative disorder)

US RE39,464, Oligonucleolotides having site specific chiral phosphorothioate internucleoside linkages (*See e.g.* Claims 46 and 47: using ICAM model for treatment of inflammatory disorder)

US 6,599,741 Modulating transcription of genes in vascular cells (*See e.g.* Claims 13, 30 and 32: using ICAM for treatment of proliferative disorder)

Therefore, in light of the state of art at the filing date of the present application, the disclosure of the present application clearly establishes a reasonable correlation between the HUVAC assay and the treatment of the claimed diseases. With this assay, and with the other information

provided in the specification, it is submitted that this factor weighs in favor of the applicants.

F. The existence of working examples. The Examiner alleges that there is no working example of treatment of any disease in human or animals. *See* Official Action, page 4. However, it is well settled that the enablement requirement does not turn on whether an example is disclosed. MPEP 2164.02. Furthermore, the courts have noted that the specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue experimentation. *See, e.g., In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). The present application has provided a detailed Examples section on pages 41 through 178 of the specification. The Examples section illustrates the synthesis of the claimed compounds and a straightforward screening assay. Therefore, applicants respectfully submit that the presence or absence of working examples with respect to on one particular aspect of the invention does not weigh against applicants.

G. Quantity of experimentation necessary. It is alleged that a large quantity of experimentation is necessary in the present case because the of use of particular claimed compounds would require the synthesis of compounds, screening the compounds for biological activity, formulation into suitable dosage, and subjecting the compounds to clinical trials with a number of fundamental different diseases described in the claims. *See* Official Action, page 3.

Applicants respectfully disagree. The courts have emphasized that "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely *routine*, or if the specification in question provides a *reasonable* amount of guidance with respect to the direction in which the experimentation should proceed.'" *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). The courts have also noted that time and expenses are merely factors in this consideration and are not the controlling factors. *United States v. Telectronics Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989).

As discussed above, the present application provides detailed guidance on synthesizing the claimed compounds (*See* paragraphs [0112] to [0298]), screening the compounds for biological activity (*See* biological assay described on pages 177 and 178 and the discussion above regarding the correlation between the biological assay and the claimed treatments), and

formulation into suitable dosage (*See* paragraphs [0078] to [0108]). Further, the assay described on page 177 and 178 is amenable to high-though-put screening which enables one of ordinary skill in the art to expeditiously screen a large number of compounds within a reasonable time period. In addition, the synthesis of compounds, biological activity screening, formulation and clinical trials all comprise routine experimentation for practitioners skilled in their respective arts. Therefore, it is submitted that the quantity of experimentation needed to make or use the invention based on the disclosure is reasonable.

Conclusion regarding enablement. The Examiner's determination of whether the enablement requirement is satisfied must consider all the evidence related to each of above eight factors and any conclusion of non-enablement must be based on the evidence as a whole. *In re Wands*, 858 F.2d, 731, at 737, 740, 8 USPQ 2d 1400, at 1404, 1407 (Fed. Cir. 1988).

When the evidence as a whole is considered, applicants respectfully submit that the claimed invention does not require undue experimentation, and thus claims 29-32, 60 and 88-100 satisfy the requirement for enablement. Applicants therefore respectfully request that the rejection be withdrawn.

Double Patenting

Claims 1-32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-12 of co-pending Application No. 11/344,534.

Claims 60, and 88-100 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-28 of co-pending Application No. 10/753261.

As the Examiner has acknowledged, the rejections are provisional rejections because the claims of the co-pending applications have yet been allowed. Applicants respectfully request the withdrawal of the rejections on this basis, with the understanding that, should claims issue in either of these applications before allowable subject matter is identified in the present application, applicants will address this double-patenting issue if one arises at that time.

Conclusion

Having addressed all of the outstanding rejections in this case, it is respectfully submitted that this application is in condition for allowance, which action is respectfully requested.

Respectfully submitted,

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